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Recent findings on astrocyte and microglia impairment and mitochondrial dysfunction in cadmium-induced inflammation: a review

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ABSTRACT
The rapid development of industry has led to severe cadmium (Cd) pollution. Recent studies highlight that heavy metals, such as cadmium, accumulate within the food chain, exacerbating the public health crisis associated with these toxic substances. The health effects of cadmium exposure can manifest in both short-term and long-term contexts, significantly impacting various bodily systems. Cadmium accumulation has been correlated with neurotoxic effects that impair cognitive functions and motor skills, ultimately diminishing quality of life. The neurotoxicity of Cd is complex – it affects neurons, astrocytes, and microglia, resulting in the disruption of central nervous system homeostasis. Cadmium activates microglia and induces inflammation in astrocytes primarily through the TLR4/NF-kB pathway, leading to increased production of TNF-α and IL-6. The neurotoxic effects of Cd are also a result of increased oxidative stress, apoptosis initiation in astrocytes, and Cd-induced changes in mitochondrial function. Chronic Cd exposure may promote the aging of microglial cells. Microglia and astrocytes are in constant communication, a change in the function of one drives the dysfunction of the other, exacerbating inflammatory and apoptotic processes in glial cells. Additionally, due to the direct cooperation between glial cells and neurons, this will contribute to neuronal dysfunction, which may be associated with the development of neurodegenerative diseases. Future research on Cd toxicity in glial cells is needed to enhance our understanding and develop effective mitigation strategies.
Keywords: cadmium; neurotoxicity; mitochondria; inflammation.

INTRODUCTION

The rapid development of industry has led to severe cadmium (Cd) pollution. Industries such as mining, metallurgy, and manufacturing are notable sources of Cd emissions, releasing the toxic element into the air, soil, and water [1]. Specifically, it is often a byproduct of zinc smelting and other metal refining processes, and runoff from agricultural land that has been treated with Cd-laden fertilizers exacerbates soil contamination. The pervasive issue of Cd pollution has garnered increasing attention due to its significant implications for human health and the environment. Cadmium is released into ecosystems primarily through industrial processes, waste disposal, and mining activities, leading to widespread contamination of soil and water sources. Recent studies highlight that heavy metals, such as Cd, accumulate within the food chain, exacerbating the public health crisis associated with these toxic substances [2, 3]. The health effects of Cd exposure can manifest in both short-term and long-term contexts, significantly impacting various bodily systems. In the short term, inhalation of Cd dust or ingestion can lead to acute symptoms such as respiratory distress and gastrointestinal disturbances, with individuals experiencing nausea, vomiting, and abdominal pain. Over a prolonged duration, chronic exposure to Cd is particularly alarming, as it is associated with severe health issues [3].

Smoking cigarettes is one of the main sources of Cd exposure in the general population. Cadmium enters the human body through the consumption of contaminated water and food, such as vegetables grown in polluted areas. Tobacco plants readily absorb Cd from the soil, and during smoking, Cd enters the body through tobacco smoke. Smokers typically have twice the levels of Cd in their blood and body compared to non-smokers [4]. Non-smokers exposed to secondhand smoke and third-hand smoke are also at risk [5]. In non-smokers and individuals not working in environments occupationally exposed Cd, diet becomes one of the most important sources of Cd exposure (Fig. 1). Cadmium has the ability to accumulate in the human body. Moreover, the acute and chronic effects of Cd exposure necessitate a thorough understanding of its mechanisms and consequences, as evidenced by its alarming correlation with various health outcomes [6]. Its half-life in the human body is approx. 10–30 years, meaning that negative effects can accumulate and intensify over a long period [7]. The accumulation of this element in the body is associated with kidney damage, bone disorders, and cardiovascular diseases. The long-term consumption of Cd-contaminated food may lead to the onset of osteoporosis and heightened risk of cancer, illustrating the metal's extensive ramifications on human health [6].

Cadmium accumulation has been correlated with neurotoxic effects that impair cognitive functions and motor skills, ultimately diminishing quality of life. This heavy metal can traverse biological membranes and blood–brain barier (BBB) accumulate in central nervous system (CNS) leading to neuroinflammation impacting cognitive functions and neuronal integrity [8]. Studies have indicated that Cd exposure is associated with neurotoxic effects, potentially contributing to conditions such as cognitive decline and neurodegenerative diseases. The toxicity of Cd is complex – it affects neurons, astrocytes, and microglia, resulting in the disruption of CNS homeostasis. The ramifications of Cd on CNS health necessitate urgent attention to mitigate exposure and prevent long-term neurological repercussions.

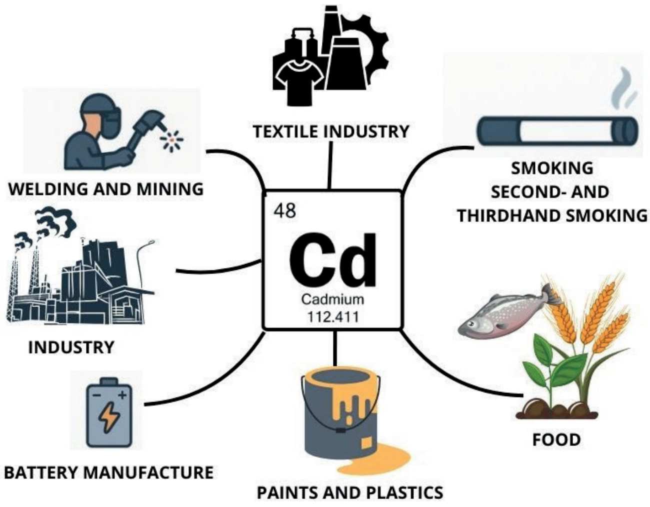

FIGURE 1. The sources of cadmium exposure

NEUROINFLAMMATION

Neuroinflammation is an inflammatory process that occurs in the CNS. It is characterized by the activation of glial cells, including microglia and astrocytes, triggered by various stimuli such as infections, injuries, or toxins [9]. During neuroinflammation, microglia become activated and secrete pro-inflammatory cytokines, including interleukin-6 (IL-6), which promotes inflammation in the brain [10]. Astrocytes maintain homeostasis in the CNS and, in response to damage or disease, can enter a reactive state known as astrogliosis. In this state, they help repair damage and limit the spread of inflammation by forming glial scars. However, when activated by pro-inflammatory factors, astrocytes themselves can also release molecules that enhance inflammation [11]. Excessive activity of reactive astrocytes can contribute to neurodegeneration by producing pro-inflammatory cytokines and free radicals, leading to neuron loss [9].

Exposure to Cd leads to dysfunction of the BBB, resulting in increased permeability. This facilitates the penetration of Cd and other substances into the CNS, where they stimulate inflammatory responses and increase oxidative stress, contributing to neuronal damage or loss [8, 12]. Cadmium causes changes in the distribution of a tight junction-associated protein, zonula occludens-1 (ZO-1), in rat brain endothelial cells, as well as the formation of F-actin stress fibers and altered vimentin positioning. These changes disrupt the organization of tight junction proteins and the cytoskeletal structure, potentially weakening the functionality of the BBB, although the expression levels of these proteins remain unchanged [13]. Cadmium-induced BBB dysfunction might also be mediated by impair function of pericytes, cells involved in the homeostasis of the BBB. Their dysfunction might influence Cd influx into the cells, since voltage-gated Ca channels of l-type responsible for Cd entry are expressed on thier plasmatic membrane [14]. Compromised BBB allows penetration of toxic substances to CNS, exacerbating neuroinflammatory processes.

CADMIUM TOXICITY IN ASTROCYTES

Astrocytes are glial cells that nourish neurons and remove waste products. They are responsible for forming the BBB, regulate pH and ion concentrations, maintaining a stable environment for proper nervous system function. Cadmium induces inflammation in astrocytes by activating the nuclear factor kappa B (NF- κB) signaling cascade, leading to increased secretion of pro-inflammatory cytokines (IL-6, TNF-α). Increased BBB permeability and the associated inflammatory response allow harmful substances to enter the CNS, potentially causing tissue damage [15, 16].

Also, astrocytes influence synaptic plasticity by controlling both the formation and elimination of synapses, as well as support the production of neurotransmitters [17]. Cadmium neurotoxicity also manifests in the disruption of glutamate transport from the extracellular space by astrocytes. Cadmium can interfere with the function of glutamate transporters in these cells, such as EAAT1 and EAAT2, and the glutamate aspartate transporter, leading to reduced uptake [18, 19]. Glutamate is the main excitatory neurotransmitter in the brain, which can lead to excessive activation of NMDA receptors and potentially cause neuronal damage [20].

Moreover, astrocytes play a vital role in regeneration and phagocytosis in CNS. In damaged brain regions, if the tissue loss is not extensive, they form glial scars. Reactive astrocytes, which appear in response to injuries, infections, ischemia, or neurodegenerative diseases, change their appearance and functions [21]. These changes include cell body hypertrophy, elongation, cell polarization, and the appearance of fibrous structures. Reactive astrocytes can induce 2 different types of reactivity: A1 and A2, which have different effects on inflammation and neuron survival. As a result of these changes, astrocytes lose their original functions, potentially leading to further neural tissue damage [21, 22]. One of the factor causing the dysfunction of astrocytes is Cd. It has been shown that in children living in areas contaminated with heavy metals, including Cd, elevated levels of the protein S100B have been found in serum. This glial-specific protein is mainly secreted by mature astrocytes surrounding blood vessels and its increased expression is typically associated with nervous system damage [23].

Oxidative stress

Exposure to Cd increases oxidative stress in astrocytes. This element disrupts the function of mitochondrial antioxidant enzymes, including glutathione peroxidase, catalase (CAT), and superoxide dismutase (SOD). Superoxide dismutase accelerates the reaction of the superoxide anion (O2•–) with itself to form hydrogen peroxide (H_2O_2), which is further broken down by CAT into water and oxygen, preventing cellular damage. Glutathione peroxidase neutralizes hydrogen peroxide and other lipid peroxides, protecting cells from oxidative damage [24]. Cadmium inhibits the activity of the mentioned enzymes, resulting in the accumulation of reactive oxygen species. Additionally, Ndzvetsky et al. observed that exposure to Cd leads to a decrease in the expression of glucose-6-phosphate dehydrogenase (G6PD). This can result in reduced viability of primary astrocytes, as proper G6PD activity, an enzyme of the pentose phosphate pathway, is integral to cellular metabolism, mitochondrial activity, and essential for antioxidant defense [25]. In excessive amounts, reactive oxygen species (ROS) can cause damage to proteins, lipids, and DNA in astrocytes. Chronic oxidative stress in astrocytes prevents them from effectively regulating the homeostasis of the nervous system environment, leading to its dysregulation [26].

Apoptosis

Cadmium also initiates apoptosis in astrocytes due to the activation of ROS-dependent pathways and disturbances in Ca homeostasis. Reactive oxygen species cause damage to lipids and proteins, triggering the apoptotic cascade. Increased Ca ion concentration in the cytoplasm leads to the activation of caspases (including caspase-3), which are crucial in the apoptosis process. Additionally, Cd can decrease the levels of anti-apoptotic proteins such as Bcl-2 and increase the levels of the pro-apoptotic protein Bax in cells [27, 28]. Moreover, Cd upregulates expression of p53, p21, and p27, what might result in G0/G1 or G2/M cell cycle arrest in human astrocytes [27].

Mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) signaling pathways are essential for many cellular processes: proliferation, differentiation, and stress response. Cadmium can disrupt these pathways, leading to cell function dysregulation. Increased activity of the aforementioned factors can result in rapid and uncontrolled oxidative stress and increased apoptosis in astrocytes. It can also disrupt communication between astrocytes and other glial cells, adversely affecting nervous tissue function [29].

Mitochondria function

Cadmium also affects the functioning of mitochondria, which are the main sites of ATP production. This heavy metal reacts with mitochondrial proteins, disrupting electron flow in the respiratory chain, leading to inefficient ATP production. As a result, ROS begin to accumulate in the cell's energy centers, increasing oxidative stress. Cadmium also inhibits mitochondrial enzymes, such as succinate dehydrogenase, disrupting the Krebs cycle. Dysfunctional mitochondria result in reduced available ATP and lead to apoptosis through the release of cytochrome C, which enhances the activity of the aforementioned caspases [12, 29].

Cadmium can influence the permeability of the cell membrane to Ca^{2+}, acting as an antagonist of L-type Ca channels, thereby disrupting the flow of these ions into cells. Additionally, Cd can interfere with the function of Ca^{2+} ATPases, which are responsible for removing Ca ions from the cytoplasm. Increased Ca^{2+} concentration within astrocytes disrupts Ca-dependent cellular signaling, affecting microvascular circulation and communication between neurons and astrocytes. Calcium in astrocytes is also crucial for the release of mediators such as prostaglandin E and nitric oxide, which impact brain function [12, 30, 31].

Neurotoxic effects of Cd exposure might be useful in cancerous tissue elimination. Cadmium in combination with arsenic (As) and lead at appropriate concentrations, induces cytotoxicity in C6 malignant glial tumor cells through molecular mechanisms involving mitochondrial stress, caspase activation, and inflammatory signaling. At concentrations of 2.5–10 μM, Cd induced apoptosis in a mitochondria-dependent manner [28]. The process was mediated by the activation of astroglia, as confirmed by increased GFAP expression and enhanced inflammatory response involving IL-1 and its receptor IL-1R1. The combination of As, Cd, and lead (Pb) activates the P38-MAPK signaling pathway, enhancing apoptosis through a mechanism independent of ERK and JNK-MAPK, which contrasts with the processes observed in primary astrocytes. Despite promising results, further studies are necessary to fully verify the efficacy and safety of this strategy [28].

Considering that microglia and astrocytes interact with each other, it is speculated that oxidative stress induces astrocytes to release pro-inflammatory cytokines, which in turn activate microglial cells [32].

CADMIUM TOXICITY IN MICROGLIA

Microglial cells are considered some of the most versatile cells in the human body. They have the ability to morphologically and functionally adapt to changing environments, which is a crucial factor in maintaining CNS homeostasis [15]. They are the primary line of defense for the CNS against unwanted changes, making the study of Cd's impact on microglia very important [33]. Depending on their location, microglial cells vary in morphology. In their resting state, they can be described as branched structures. In cases of inflammation or injury, they can become activated, leading to the formation of thicker, shorter processes and increased volume. Under pathological conditions, these cells can also function as phagocytes [16]. Different forms of activation not only change their morphology but also their lysosomal content, electrophysiological parameters, and gene profiles [34, 35]. There are 2 key types of microglial cell activation: M1, which exhibits neurotoxic potential, and M2, which is characterized by neuroprotective potential. M1 cells secrete reactive oxygen and nitrogen species, TNF-α, IL-1β, and IL-12, which are pro-inflammatory factors [12]. In contrast, M2 cells produce trophic factors such as transforming growth factor-beta and brain-derived neurotrophic factor. Brain-derived neurotrophic factor influences the regulation of key physiological and pathological functions in the body, including neuron development, learning processes, apoptosis, neurogenesis, and neuroregeneration [31]. Cadmium, upon entering microglia, causes their activation. Resting microglia monitor the brain environment, waiting for potential damage signals [36]. Cadmium triggers a strong response, mainly through the TLR4/NF-kB pathway. Toll-like receptors (TLR), especially TLR4, are crucial for detecting pathogens and damage in cells. Cadmium strongly modulates these receptors, initiating a signaling cascade that activates NF-κB, a key transcription factor regulating the expression of pro-inflammatory genes. This leads to increased production of cytokines such as TNF-α and IL-6, which cause inflammation [37, 38]. These cytokines induce neuron death primarily through apoptosis and necrosis mechanisms. Tumor necrosis factor-alpha activates TNFR1 receptors on neurons, thereby inducing a signaling cascade that activates caspases [39].

Oxidative stress

Cadmium accumulates in microglial cells, leading to dose-dependent cytotoxicity. Cadmium significantly increases oxidative stress levels in cells by activating NF-κB and activator protein 1 (AP-1). Additionally, increased expression of genes related to oxidative stress response, such as metallothionein, heme oxygenase-1, and glutathione S-transferase P, has been observed [38]. Excessive accumulation of ROS leads to cellular damage. Under physiological conditions, microglia utilize antioxidant mechanisms, such as SOD and glutathione, to neutralize ROS. However, Cd inhibits these mechanisms, leading to ROS accumulation, lipid peroxidation, and damage to proteins and DNA [38, 40, 41]. Lipid peroxidation in cell membranes causes destabilization and increased permeability, further exacerbating cellular damage [42]. Reactive oxygen species also act as secondary inflammatory mediators, meaning their excess activates inflammatory pathways, deepening brain inflammation [43].

Autophagy

Cadmium disrupts the process of autophagy in microglia. Autophagy is a key mechanism for removing damaged organelles and proteins, maintaining cellular homeostasis. Cadmium inhibits autophagy by disrupting the function of the mTOR (mammalian target of rapamycin) pathway, which is the main regulator of this process [44]. Disruption of autophagy leads to the accumulation of damaged mitochondria and other organelles, which exacerbates oxidative and inflammatory stress [45]. The accumulation of damaged mitochondria and disruption of their function leads to abnormalities in the respiratory chain, intensifying the production of ROS, creating a vicious cycle where oxidative stress and inflammation mutually reinforce each other [12]. Ineffective autophagy can also lead to the activation of apoptotic mechanisms, promoting the death of microglial cells and neurons [46].

Mitochondria function

Cadmium also causes morphological changes in mitochondria by disrupting their fusion and division controlled by mitofusin 2 [47]. It adversely affects processes related to Ca ion function by binding to ion receptors, destabilizing Ca^{2+}-dependent cellular processes. Calcium is a crucial signaling ion in neurons and microglia, controlling many cellular processes, including inflammatory response, ROS production, and apoptosis. Cadmium blocks L-type Ca receptors causing excessive Ca^{2+} influx into cells [46, 48]. Increased intracellular Ca concentration activates degradative enzymes: phospholipases, endonucleases, and proteases. This contributes to the destruction of lipids, proteins, and nucleic acids [41].

Von Leden and colleagues proposed a theory suggesting that aging cells are chronically in a pro-inflammatory state. Therefore, the impact of Cd on microglia might promote the aging of these cells, thus disrupting their proper functioning [49]. Cadmium-activated microglia release toxic cytokines and ROS, which directly damage neurons. Particularly toxic are pro-inflammatory cytokines, which can induce apoptosis in neurons. Chronic release of factors, such as TNF-α, IL-1β, and IL-6, leads to long-term neurotoxicity, causing neuron degeneration and death [32]. In the context of long-term Cd exposure, such processes may contribute to the development of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, or amyotrophic lateral sclerosis [50].

Microglia and astrocytes are not indifferent to each other's actions [51]. Hence, the inflammatory activation of astrocytes by Cd will cause oxidative stress, leading to the release of pro-inflammatory cytokines that will activate microglial cells [32].

CONCLUSIONS

Cadmium pollution possesses significant risks to human health, specifically affecting the CNS and contributing to various diseases. Cadmium exposure increases the permeability of the BBB, allowing harmful substances to enter the CNS and potentially cause tissue damage. Cadmium activates microglia and induces inflammation in astrocytes primarily through the TLR4/NF-κB pathway, leading to increased production of pro-inflammatory cytokines such as TNF-α and IL-6. The neurotoxic effects of Cd are also a result of oxidative stress, which is induced by increased levels of ROS and the inhibition of antioxidant mechanisms in microglia and astrocytes. Chronic oxidative stress prevents astrocytes from effectively regulating nervous system homeostasis, resulting in lipid peroxidation and cellular damage.

Cadmium also initiates apoptosis in astrocytes through ROS-dependent pathways and disturbances in Ca homeostasis. Cadmium-induced changes in mitochondrial function and Ca ion processes further contribute to cellular damage. Additionally, Cd disrupts autophagy by affecting the mTOR pathway, leading to the accumulation of damaged organelles and exacerbating oxidative and inflammatory stress. Chronic Cd exposure may promote the aging of microglial cells, disrupting their function and leading to the release of toxic cytokines and additional ROS, which damage neurons and contribute to neurodegenerative diseases (Fig. 2).

The interaction between microglia and astrocytes under Cd exposure results in oxidative stress and the release of pro-inflammatory cytokines, further activating microglial cells and deepening brain inflammation. Since microglia and astrocytes are in constant communication, a change in the function of one drives the dysfunction of the other, exacerbating inflammatory and apoptotic processes in glial cells. Additionally, due to the direct cooperation between glial cells and neurons, this will contribute to neuronal dysfunction, which may be associated with the development of neurodegenerative diseases.

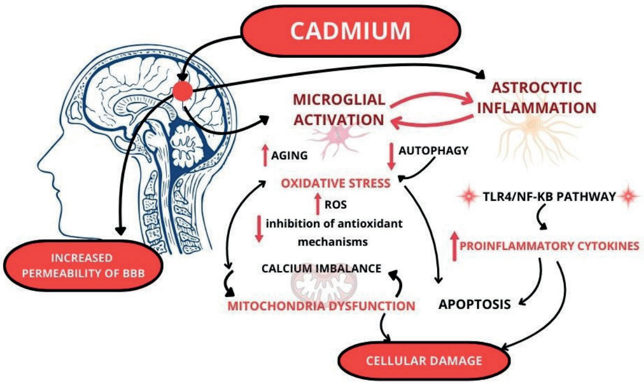

FIGURE 2. The mechanisms underlying neuroinflammatory properties of cadmium

FUTURE DIRECTIONS IN CADMIUM RESEARCH

The study of Cd has increasingly revealed critical challenges and potential avenues for future research, particularly concerning its environmental impact and health implications. Future research on Cd toxicity in glial cells should focus on several key areas to enhance our understanding and develop effective mitigation strategies. Investigating the detailed molecular and biochemical pathways through which Cd induces oxidative stress, inflammation, and apoptosis in glial cells is crucial for identifying potential therapeutic targets. Research is needed on the role of Cd-induced glial cell dysfunction in the development and progression of neurodegenerative, potentially leading to new approaches for prevention and treatment. Researching potential protective agents and strategies to mitigate Cd toxicity in glial cells, including antioxidants, anti-inflammatory drugs, and compounds that enhance autophagy and mitochondrial function, seems to be the most vital.

Assessing the broader environmental and public health implications of Cd exposure, particularly in populations living in contaminated areas, is also important. This includes studying the effects of chronic low-level exposure and developing policies for reducing Cd pollution. By addressing these areas, future studies can significantly advance our understanding of Cd toxicity in glial cells and contribute to the development of effective interventions to protect CNS health.

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